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The role of explicit solvent molecules in the calculation of NMR chemical shifts of glycine in water

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Abstract We present the results of a computational study of the NMR properties of glycine in water solution at the level of density functional theory employing the B3LYP functional and the 6-31G(d,p) and pcSseg-2 basis sets, describing the solvent either via the PCM continuous solvation model or PCM with additional explicit water molecules hydrogen bonded to the solute. We observe that the solvent causes considerable changes in the predicted magnetic shieldings and that the results depend significantly on the number of solvent molecules included in the quantum mechanical treatment.

Keywords Chemical shift · PCM · pcSseg-2 basis sets

1 Introduction

Amino acids are some of the fundamental bricks of life carrying out much of the functions in cells and therefore in living organisms. Glycine, in particular,

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is the smallest amino acid allowing a great diversity of theoretical studies, [1–14] which is stimulated by the fact that some of its properties are known experimentally. Recently the investigation on the micro complexes of water and small amino acids has gained a renewed interest in particular, as even when they are measured in gas phase there is a micro solvation of the molecule of interest.[15, 16]

Among the many studies devoted to glycine some were aimed at elucidating the mechanisms of tautomerization where the proton transfer of the neutral glycine, which is stable in the gas phase, to the zwitterionic conformer, which is stable in aqueous solution, has an estimated free energy barrier of about $7.3 \frac{\text{kcal}}{\text{mol}}$ [1–3, 5, 6, 11, 17–21]. Other recent work was aimed at studying small clusters of Gly.(H₂O)_n complexes in order to elucidate structures and binding energies [22, 23].

The three most stable conformers of neutral glycine in gas phase were determined by Császár [24], Godfrey *et al* [25], Sauer *et al* [7], and Aikens and Gordon [26]. In this work we found the same three structures in the same energetic order as in the previous studies with the exception of Godfrey *et al* [25]. The second most stable neutral conformation (N) is depicted in Figure 1 (left), where the C–N and O–H bonds are antiperiplanar to the C=O bond. Of the three most stable neutral conformers only this structure is converted to the zwitterion (Z), shown in Figure 1 (right). The latter can be obtained from the corresponding N conformer by geometry optimization using the Polarizable Continuum Model (PCM). These two structures are respectively the most stable geometries we found for N- and Z-glycine when including a continuum polarizable medium.

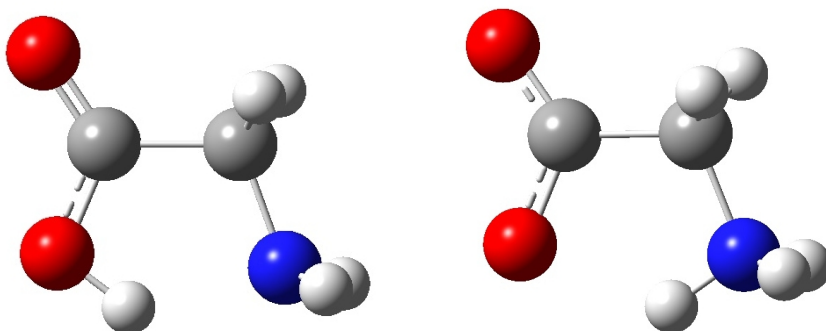


Fig. 1 Optimized geometries of neutral (left) and zwitterionic (right) glycine forms using B3LYP/6-31G(d,p)

The purpose of this work is to investigate the NMR properties of glycine in water solution, studying in detail the applicability of the PCM continuous solvation model approximation [27–34], as compared to the introduction of explicit hydrogen-bonded (HB) solvent molecules in calculations of NMR nuclear shieldings .

2 Computational details

All the calculations were carried out with Gaussian09 program [35], using density functional theory (DFT) with the B3LYP exchange correlation [36, 37], in a liquid solvent described by the PCM approximation [38].

Calculations of the structures and energies of the complexes were carried out with the 6-31G(d,p) basis set, with 120 and 25 basis functions for the glycine and water molecules, respectively [39, 40]. The geometry optimizations were started from several conformers and explicit solvent molecule positions. Each additional water molecule was placed so that it could form at least one hydrogen bond to a vacant hydrophilic site in glycine. For each case, about 20 different starting positions consistent with the HB criterion in Ref. [6] were tried in order to reduce the risk of ending in a local minimum during the optimization procedure. In practice, most of the starting configurations converged nevertheless to the same single geometry.

Calculations of the nuclear magnetic shieldings were performed using Gaussian09 both at the same level of the theory as mentioned above and with a specialized basis set, namely pcSseg-2 for shieldings [41].

The theory of nuclear shielding constants (σ) [42] and different computational methods for calculating them have been described extensively in the literature [43–46]. In the present work they were calculated employing the gauge including atomic orbitals (GIAOs) method [47] due to its reduced basis set dependence as compared to e.g. the CTOCD-DZ method [48, 49].

The magnetic properties depend on the number of explicit water molecules taken into account, which we vary from zero to a full first solvation layer. Considering only H₂O molecules directly hydrogen-bonded to the solute, the number of solvent molecules necessary to reach saturation of the two hydrophilic groups of glycine (the amino and the acidic ends) vary a bit according to the conditions established for the hydrogen bond formation. Following Campo [6], we require a maximum distance of 2 Å between donor and acceptor of the glycine and water molecules for a hydrogen bond, and a minimum angle of 145° formed by the atoms X_{donor}–H–Y_{acceptor}, where X and Y are either both oxygen atoms, or an oxygen and a nitrogen atom.

3 Results

The NMR properties for glycine in water solution can be calculated by accounting for solvent effects on average using the PCM solvation model. An approach to study the consistency of these predictions consists in comparing the results to those obtained by incorporating explicit water molecules hydrogen-bonded to glycine and embedding the ensuing complex in the continuous, homogeneous and polarizable medium of PCM. The positions where water molecules can be hydrogen-bonded to glycine are found by searching for stable local energy minima structures, that pass the frequency test.

3.1 Structures of hydrogen-bonded complexes

Basically four hydrophilic sites were identified in N-glycine: the *trans* and *cis* oxygen atoms, i.e. anti- or syn-periplanar to the C-N bond, (henceforth respectively denoted as OT and OC), the hydrogen atoms in the amino group (HN) and a water molecule simultaneously hydrogen-bonded to the carboxylic hydrogen and the nitrogen atom in the amino group (AA):

- | | |
|--------------------------------|--|
| (1) OT, <i>trans</i> -oxygen: | $\text{H}-\text{O}-\text{H} \cdots \text{O}=\text{C}$ |
| (2) OC, <i>cis</i> -oxygen: | $\text{H}-\text{O}-\text{H} \cdots (\text{OH})-\text{C}=\text{O}$ |
| (3) HN, amino group hydrogen: | $\text{H}_2-\text{O} \cdots \text{H}-\text{N}$ |
| (4) AA, acid and amino groups: | $\text{C}-\text{O}-\text{H} \cdots (\text{OH})-\text{H} \cdots \text{N}$ |

Although the last case actually comprises two hydrophilic positions, all attempts to find a local energy minimum with a solvent molecule bonded to only one of these positions resulted in a H_2O molecule hydrogen-bonded to both sites. The positions of the four hydrophilic sites are depicted in Figure 2.

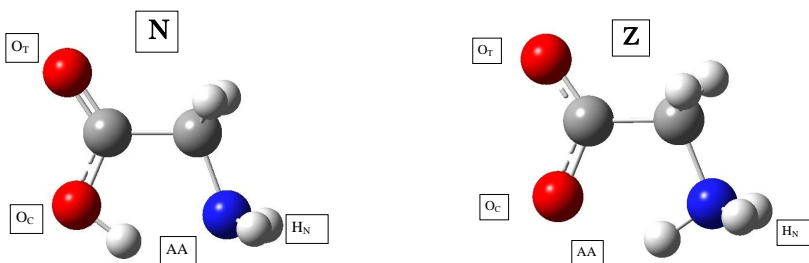


Fig. 2 Diagram of the possible H-bond sites between glycine-N/glycine-Z in water

In the case of the zwitterionic conformer the situation is similar, the only differences being that the *cis*-oxygen (OC) is no longer protonated, and that the doubly hydrogen-bonded case (AA) now corresponds to simultaneous bonds to an aminonium hydrogen atom and to the *cis*-oxygen.

Glycine, in either its N- or Z- conformer, has five magnetically distinct positions occupied by non-hydrogen nuclei: the *cis* and *trans* oxygen atoms, the carboxylic and methylenic carbon atoms, and the nitrogen atom. In the following these are respectively denoted as O_c , O_t , C_c , C_m , and N.

3.2 Nuclear magnetic shieldings for the non-hydrogen nuclei in glycine in water solution

The nuclear magnetic shieldings for the non-hydrogen nuclei in glycine in water solution calculated at the DFT/B3LYP level within the PCM continuous solvation model and the pcSseg-2 basis set are summarized in Table 1 for the

N- and Z-conformers. The table also shows, for future reference, the magnetic shieldings calculated with the smaller 6-31G(d,p) basis set. As expected for absolute shieldings, the results differ substantially between the two cases. However, the relevant property, i.e. the chemical shift between the two conformers exhibits a much small basis set dependence of 1-4 ppm apart from O_c with 11 ppm.

Table 1 Absolute nuclear magnetic shieldings (in ppm) for the non-hydrogen nuclei in glycine in water solution calculated at the DFT/B3LYP level using PCM with the pcSseg-2 and 6-31G(d,p) basis sets

Conformer	Basis Set	C_c	C_m	N	O_c	O_t
N-Glycine	6-31G(d,p)	15.0	147.9	240.5	128.9	13.2
	pcSseg-2	-17.2	131.8	226.3	97.5	-34.3
Z-Glycine	6-31G(d,p)	23.0	146.6	226.6	45.2	52.5
	pcSseg-2	-8.5	130.8	209.0	2.9	9.0

The reliability of the PCM approach to describe the surrounding solvent medium can be tested by incorporating water molecules until saturation of all possible hydrophilic sites. It is interesting to see how this process evolves while adding solvent molecules one-by-one, i.e. to see at what point an asymptotic regime is reached. Our procedure was sequential. First, we found that for N-glycine the most stable Gly.(H₂O) complex calculated with PCM corresponds to a H₂O molecule occupying the OT position. Next we looked for the Gly.(H₂O)₂ complex with lowest energy having at least one water molecule at the OT position. In this way, the procedure was continued, where the most stable Gly.(H₂O)_n structure was obtained while respecting the configuration of the previously found Gly.(H₂O)_{n-1} complex. We found that a total of $n = 8$ water molecules can be added having each at least one HB to N-glycine. The result of sequentially occupied hydrophilic positions is OT, OC, AA, OC, HN, OT, HN, OT. This means that, upon saturation, the number of water molecules hydrogen-bonded to the OT, OC, HN and AA hydrophilic sites of N-Glycine are 3, 2, 2 and 1, respectively. The geometries of these complexes can be found in the supplementary material.

Tables 2 and 3 present the cumulative changes in the predicted shieldings in N- and Z-glycine with respect to the bare PCM calculation, $\Delta\sigma_n = \sigma[\text{Gly}(\text{H}_2\text{O})_n] - \sigma[\text{Gly}]$, as explicit solvent molecules hydrogen-bonded to glycine in a PCM environment are included in the quantum mechanical treatment. Our calculations include as limiting values the complexes Gly.(H₂O)₉ and Gly.(H₂O)₁₀, where the water molecules beyond $n = 8$ are solely H-bonded to solvent molecules. The results are presented graphically in the left panels of Figures 3, 4 and 5 for the N- C_c - C_m , O_c and O_t nuclei for N-glycine and in the right panels for Z-glycine.

Table 2 The magnetic shielding (in ppm) for the non-hydrogen nuclei in N-glycine in water solution: difference between the results using n and zero explicit solvent molecules both in a PCM environment calculated using the pcSseg-2 basis set.

Hydrophilic site	$n(\text{H}_2\text{O})$	C_c	C_m	N	O_c	O_t
OT	1	-1.5	0.1	0.1	-3.4	5.7
OC	2	0.2	0.0	-0.2	-4.2	1.3
AA	3	1.0	-5.0	-5.5	-12.7	-27.9
OC	4	1.6	-5.1	-5.6	-14.6	-38.7
HN	5	1.1	-4.5	-7.5	-15.0	-36.4
OT	6	-0.8	-4.1	-7.7	-19.4	-28.9
HN	7	-0.8	-3.8	-9.3	-18.2	-32.4
OT	8	-3.0	-4.1	-9.1	-24.5	-27.1
Ext	9	-3.1	-4.0	-9.4	-23.8	-24.2
Ext	10	-2.6	-3.9	-10.3	-21.3	-30.4

Table 3 The magnetic shielding (in ppm) for the non-hydrogen nuclei in Z-glycine in water solution: difference between the results using n and zero explicit solvent molecules both in a PCM environment calculated using the pcSseg-2 basis set.

Hydrophilic site	$n(\text{H}_2\text{O})$	C_c	C_m	N	O_c	O_t
AA	1	-1.5	-0.7	-0.6	-0.5	-11.7
OT	2	-1.7	-0.5	-0.1	-5.6	-10.3
OC	3	-1.8	-0.5	-0.2	-7.9	-10.1
HN	4	-2.2	0.3	-1.4	-4.2	-15.7
OC	5	-2.9	0.6	-2.7	-1.7	-23.0
OT	6	-3.8	0.3	-1.6	-3.6	-27.1
HN	7	-4.4	1.3	-3.5	-3.5	-24.5
OT	8	-5.4	1.1	-3.4	-13.7	-20.9
Ext	9	-5.8	1.1	-3.4	-14.3	-20.0
Ext	10	-5.7	1.0	-3.3	-12.3	-21.1

Figures 4 and 5, in addition to the analysis with the pcSseg-2 basis set (solid line), include the values calculated with the smaller 6-31G(d,p) basis set (dashed line). It is satisfying to see that the results for $\Delta\sigma_n$ are very similar for both basis sets, indicating that the larger set is not essential for evaluating the validity of PCM as a description of the solvent.

The pattern that emerges as water molecules are added to the four hydrophilic positions is that the predicted shieldings in the end always decrease or in the single case of C_m in Z-glycine stay basically constant. Furthermore, the shieldings tend to converge with increasing number of explicitly considered solvent molecules, maybe with the exception of O_t in the N-conformer. In both conformers the largest effect is observed for O_t and O_c . The *trans*-oxygen is

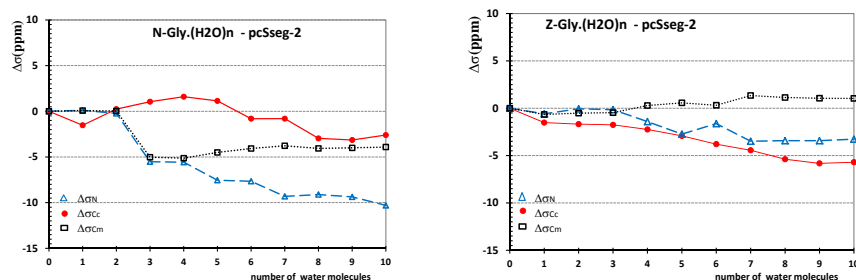


Fig. 3 Change in the magnetic shieldings (in ppm) of the carbon and nitrogen nuclei for N- (left) and Z- (right) glycine in water solution, as explicit solvent molecules are incorporated in the calculation, using the pcSseg-2 basis set.

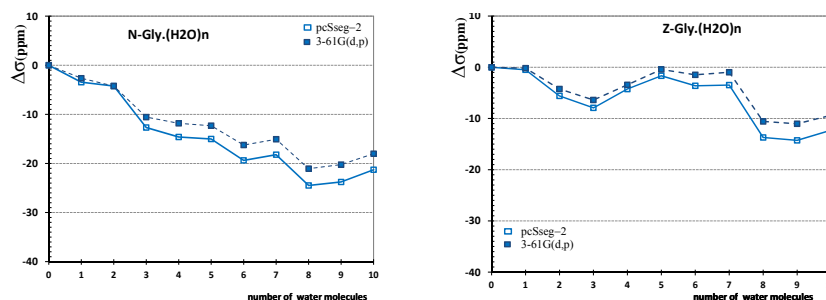


Fig. 4 Change in the magnetic shieldings (in ppm) of *cis*-oxygen for N- (left) and Z- (right) glycine in water solution, as explicit solvent molecules are incorporated in the calculation, using the pcSseg-2 (solid line) and the 3-61G(d,p) (dashed line) basis sets.

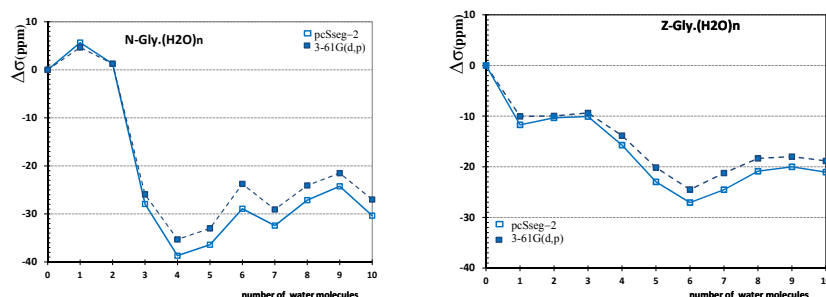


Fig. 5 Change in the magnetic shieldings (in ppm) of *trans*-oxygen for N- (left) and Z- (right) glycine in water solution, as explicit solvent molecules are incorporated in the calculation, using the pcSseg-2 (solid line) and the 3-61G(d,p) (dashed line) basis sets.

the most sensitive to the presence of explicit water molecules and thus the nucleus, where the disagreement with the bare PCM prediction is the largest.

For the N-conformer the O_t nucleus is systematically shielded (deshielded) when adding solvent molecules at position OT (OC), with an average change of +6 ppm (−6 ppm). The positive value is the expected behavior for an electronegative atom when hydrogen-bonded to hydrogen. Addition of H_2O to

the AA position brings about a large deshielding effect ($\Delta\sigma = -26$ ppm), a result that we find surprising. The *cis*-oxygen is mainly affected by explicit water molecules at the AA and OT sites, with deshieldings of $\Delta\sigma = -7$ and $\Delta\sigma \simeq -4$ respectively, for a global change of $\Delta\sigma = -20$ ppm. The decrease in shielding is smaller but also significant for nitrogen ($\Delta\sigma = -8$ ppm), driven by the inclusion of explicit water molecules at the AA ($\Delta\sigma = -4$ ppm) and HN ($\Delta\sigma = -2$ ppm) positions. The effect on the carbon nuclei is smaller, $\Delta\sigma = -3$ ppm for C_m (only H_2O at AA is relevant) and $\Delta\sigma = -2$ ppm for C_c because of cancelations between the contributions of water at the OT and OC sites.

For the Z-conformer, the distribution of solvent molecules at the hydrophilic sites is the same, but the order in which they are occupied differs, as detailed in Table 3. The two main effects are a reduction in shielding of -19 ppm and -10 ppm for the *trans* and the *cis*-oxygen nuclei, respectively. The total result for O_t arises from three negative contributions, AA ($\Delta\sigma \simeq -10$), OC ($\Delta\sigma \simeq -5$ ppm) and HN ($\Delta\sigma \simeq -1$ ppm), and one positive, OT ($\Delta\sigma \simeq +2.5$ ppm). The global result for O_c is smaller because of comparable positive and negative contributions, OT ($\Delta\sigma \simeq -6.5$ ppm) and HN ($\Delta\sigma \simeq +4$ ppm). For the carboxyl carbon the total change is $\Delta\sigma \simeq -5$ ppm with comparable contributions from water at each site, for the methylenic carbon the effect is negligible, and for nitrogen it is $\Delta\sigma \simeq -1$ ppm where the only contribution is from the HN site.

Summarizing we find that in particular for the oxygen nuclei, but also for nitrogen the converged results with explicit hydrogen-bonded water molecules differ substantially from the PCM only results, meaning that the continuous polarizable medium approximation is not adequate for predicting NMR shieldings of a solution of glycine in water. The effect is thought larger for the neutral conformer than for the zwitterionic structure.

3.3 Influence of water molecules at each hydrophilic site on the nuclear magnetic shieldings

The results in Tables 2 and 3 report the change in the predicted magnetic shieldings when adding to the quantum region a water molecule hydrogen-bonded to the hydrophilic sites in a particular $Gly.(H_2O)_n$ complex. In this section we discuss how $\Delta\sigma(I, J)$, the change in the magnetic shielding at nucleus I ($I = O_c, O_t, C_c, C_m, N$) when adding an explicit hydrogen-bonded solvent molecule at hydrophilic site J ($J = OC, OT, HN, AA$), depends on the presence of other solvent molecules hydrogen-bonded to the solute.

We thus consider the changes in the shielding brought about by the addition of H_2O to the same hydrophilic site in different $Gly.(H_2O)_n$ complexes, with $n = 0, 7$. Furthermore we have to consider that, for a given value of n , there are several possible distributions of the n solvent molecules around glycine. For instance, we find 9 distinct $Gly.(H_2O)_3$ complexes to which a H_2O molecule can be added at the OT site, yielding 9 different $Gly.(H_2O)_4$

complexes and thus nine $\Delta\sigma(I, \text{OT})$ results for each nucleus I . Considering all values of n , this amounts to a total of 31 different complexes to which an additional solvent molecule can be added at the OT site.

In order to summarize the values of $\Delta\sigma(I, J)$, we have computed $(\Delta\sigma)_i$ for each possible starting structure, and evaluated their sample mean $\langle\Delta\sigma\rangle$ and standard deviation SD,

$$\langle\Delta\sigma\rangle = \frac{\sum_{i=1}^m (\Delta\sigma)_i}{m}$$

$$\text{SD} = \sqrt{\frac{\sum_{i=1}^m [(\Delta\sigma)_i - \langle\Delta\sigma\rangle]^2}{m-1}}$$

Here m is the total number of different Gly.(H₂O) _{n} complexes ($n = 0, 7$) to which an additional solvent molecule can be added at the J site. The values of m are 28, 31, 30 and 25 respectively for the OC, OT, HN and AA hydrophilic sites.

Given the computational cost required to evaluate $\Delta\sigma$ for the large number of possible Gly.(H₂O) _{n} complexes, and the fact that the predictions of $\Delta\sigma$ have been found to be similar for the pcSseg-2 and 6-31G(d,p) basis sets, we used the latter for the studies presented in this section.

Tables 4 and 5 summarize the average change in the NMR shielding at each non-hydrogen nucleus due to the addition of H₂O molecules to the different hydrophilic sites for the N- and Z- conformers.

Table 4 The change in magnetic shielding (in ppm) for the non-hydrogen nuclei in N-glycine due to the addition of a H₂O molecule at the solute hydrophilic sites (see description in the text)

Site	C _c	C _m	N	O _c	O _t
HN	-0.5 ± 0.5	0.4 ± 0.1	-2.3 ± 0.9	-1.7 ± 1.8	1.0 ± 2.4
AA	1.2 ± 0.3	-4.3 ± 0.3	-2.9 ± 1.3	-4.7 ± 2.1	-31.9 ± 2.2
OC	0.7 ± 0.8	-0.1 ± 0.2	-0.2 ± 0.7	-1.5 ± 1.2	-3.8 ± 2.9
OT	-1.3 ± 0.6	-0.1 ± 0.3	0.2 ± 0.6	-2.4 ± 1.8	3.6 ± 3.1

For the N- conformer, the largest change corresponds to the addition of H₂O at the AA site. Its effect is to deshield all nuclei (mainly O_t), with the exception of a small increase in the shielding of C_c. It is noteworthy that the values obtained for $\Delta\sigma(I, \text{AA})$ are largely independent from the starting Gly.(H₂O) _{n} complex. In effect, the standard deviation of the results is 28%, 5%, 23%, 35% and 7% of the values of $\Delta\sigma$ for the C_c, C_m, N, O_c, O_t nuclei, respectively. Another indication of the relative irrelevance of preexistent hydrogen-bonded solvent molecules to the changes caused by the addition

Table 5 The change in magnetic shielding (in ppm) for the non-hydrogen nuclei in Z-glycine due to the addition of a H₂O molecule at the solute hydrophilic sites (see description in the text)

Site	C_c	C_m	N	O_c	O_t
HN	-0.8 ± 0.3	0.8 ± 0.5	-1.8 ± 1.0	0.7 ± 3.0	-1.1 ± 2.3
AA	-1.1 ± 0.5	-0.5 ± 0.7	-0.7 ± 1.1	-0.5 ± 2.4	-9.3 ± 3.7
OC	-0.5 ± 0.6	-0.1 ± 0.8	0.1 ± 1.2	2.3 ± 3.7	-6.9 ± 4.7
OT	-0.4 ± 0.5	-0.2 ± 0.7	0.1 ± 1.0	-5.0 ± 4.5	0.9 ± 2.8

of a water molecule, is that the fluctuations in $\Delta\sigma$ are always smaller than the average $\langle\Delta\sigma\rangle$, with the exception of the few cases where $\langle\Delta\sigma\rangle$ itself is very small, namely (N, OC), (N, OT), (C_m , OC), (C_m , OT) and (C_c , OC).

Addition of solvent at the HN site mainly affects the nitrogen environment with, as expected, a deshielding similar to the AA case. In what regards the oxygen nuclei, O_t is deshielded (shielded) by the addition of H₂O at the OC (OT) site, while the O_c nucleus suffers a deshielding in both cases, but smaller in absolute value.

For the Z- conformer, the changes observed when replacing the continuous description of the medium by the explicit quantum treatment of solvent molecules are smaller than for the N-conformer. The most conspicuous cases are the magnetic deshieldings for the (AA, O_t), (OC, O_t) and (OT, O_c) combinations, which we discuss next. Besides these, marginal changes are predicted for nitrogen and *cis*-oxygen when a H₂O molecule is included at the HN and OC sites, respectively.

The carboxylate ion in the zwitterionic conformer is a hybrid of two resonance structures, with the $-C-O^{-1}$ negative charge either on the *cis* or *trans* oxygen atom, and the double $-C=O$ bond on the other. Any modification that decreases the net negative charge on oxygen, and/or increases the double nature of its bonding to the carboxylic carbon atom, will reduce its magnetic shielding because of both the smaller global electronic density and the fact that π -electrons have a vanishing value for the wavefunction at the oxygen (and C_c) atom. This is in fact what we observe for O_t when adding explicit water molecules at the AA and OC sites, because the hydrogen-bonded water molecule stabilizes the negative charge at the OC site. The same mechanism explains the deshielding of O_c by H₂O at the OT site.

4 Concluding Remarks

In this work we have systematically studied the nuclear magnetic shieldings of the neutral and zwitterion conformers of glycine in water solution using a dielectric continuum model of water via the PCM model and an increasingly larger number of explicit water molecules included in the quantum mechanical treatment, where all geometrical parameters are allowed to relax.

We observed the following patterns:

- The largest effect to the magnetic shielding, in both conformers, is observed for the oxygen nuclei. The *trans* oxygen, O_t is the most sensitive to the presence of explicit water molecules, and the one where disagreement with the bare PCM prediction is the largest.
- For the N-conformer the O_t nucleus is systematically shielded (deshielded) when adding solvent molecules at position OT (OC), with an average change of +6 ppm (−6 ppm). The positive value is the expected behavior for an electronegative atom when hydrogen-bonded to hydrogen. Addition of H_2O to the AA position brings about a large unshielding effect ($\Delta\sigma = -29.2$ ppm), a result that we find surprising.
- For the Z-conformer, the two main effects are a decrease in shielding by −19 ppm and −10 ppm for the *trans* and the *cis*-oxygen, respectively. The total result for O_t arises from three negative contributions, AA ($\Delta\sigma \simeq -10$ ppm), OC ($\Delta\sigma \simeq -5$ ppm) and HN ($\Delta\sigma \simeq -1$ ppm), and one positive, OT ($\Delta\sigma \simeq +2.5$ ppm). The global result for O_c is smaller because of comparable positive and negative contributions, OT ($\Delta\sigma \simeq -6.5$ ppm) and HN ($\Delta\sigma \simeq +4$ ppm).
- The shieldings tend to converge with increasing number of explicitly considered solvent molecules and for the oxygen nuclei and to a lesser extent also for the nitrogen nucleus the results differ substantially from the PCM only result. The continuum polarizable medium approximation is thus not adequate to predict NMR shieldings of a solution of glycine in water. The solvent effects are so important that the main conclusions most likely apply to other molecular properties of glycine in water, for instance to optical properties.

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